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EDITORIAL COMMENT

Balancing the Risks of Stroke and Bleeding in Patients With Atrial Fibrillation and Renal Dysfunction*

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The growing prevalence of concurrent chronic kidney disease (CKD) and atrial fibrillation (AF) is significant, as both independently elevate the risk of thromboembolism and death. With shared risk factors and interlinked pathophysiological processes involving the renin-angiotensin-aldosterone system and cytokine upregulation, it is estimated that 30 to 60% of all patients with AF have mild to moderately reduced creatinine clearance (CrCl).[1,2] Thus, this unique patient group needs careful consideration of stroke and major bleeding risks to prevent onerous outcomes.

Vitamin K antagonists (VKAs) for stroke prevention in AF and CKD pose higher bleeding risks, with observational studies suggesting an accelerated decline in renal function.[1-3] Growing preference for direct oral anticoagulants (DOACs) exists, but limited data in moderate to severe CKD introduces uncertainty. The commercially available DOACs undergo significant degrees of renal clearance: dabigatran 80%, edoxaban 50%, rivaroxaban 33%, and apixaban 27%, translating to higher drug levels in patients with reduced CrCl. Approximately 80% of patients in the pivotal clinical trials (RE-LY, ARISTOTLE, ENGAGE AF-TIMI-48, and ROCKET AF) that contributed to the approval of DOACs had a CrCl >50 ml/min, and patients with severe CKD (CrCl <20-30 ml/min) were excluded.[4,5] Much of the knowledge supporting the use of DOACs in CKD comes from subanalyses of these landmark trials (limited by small sample size) and meta-analyses—one such analysis of 8 clinical trials and 46 observational studies showed superiority of DOACs over VKAs for both efficacy and safety in mild to moderate CKD (15-60 ml/min).[6] Another study found that Edoxaban 30 mg had the most favorable safety profile, and only dabigatran 150 mg had a more favorable efficacy profile among patients with CrCl 25 to 49 ml/min.[1] However, these comparisons are indirect with inconsistent follow-up duration, lack of individual time-to-event analysis, and no accounting for heterogeneity. A recent large network meta-analysis of 71,683 patients across a range of CrCl down to 25 ml/min showed encouraging findings: 1) standard-dose DOAC (vs VKA) was associated with significantly lower stroke and systemic embolism with a significant treatment-by-CrCl effect (4.8% decrease in hazard ratio per 10-ml/min decrease in CrCl); 2) death was lower with standard-dose DOACs; 3) no significant difference in bleeding or intracranial hemorrhage with lower-dose vs standard-dose DOAC; and 4) significantly lower intracranial hemorrhage with standard-dose DOAC over VKAs.[7]

Nonetheless, there is a lack of robust real-world data on performance of DOACs in patients with renal dysfunction. In this issue of *JACC: Advances*, Gwechenberger et al[8] report a clinically relevant subanalysis of the ETNA-AF (Edoxaban Treatment in Routine Clinical Practice With Non-valvular Atrial Fibrillation) registry—a postauthorization observational study of the real-word population. The present subanalysis included only the European patients with objectives to assess change in CrCl over a 2-year period, differences in clinical outcomes in those with and without worsening renal function (WRF),

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and to identify predictors of WRF and clinical outcomes. WRF was defined as ≥25% reduction in CrCl between baseline and 2 years, and 69% of the total enrolled patients were included in the analysis (n = 9,054). The findings are as follows: 1) WRF occurred in 9.7% of patients during the first 2 years; 2) patients with WRF had higher annualized event rates of all-cause death (3.88%/year vs 1.88%/year; $P < 0.0001$), cardiovascular death (2.09%/year vs 0.92%/year; $P < 0.0001$) and major bleeding (1.51%/year vs 0.98%/year; $P = 0.0463$); 3) rates of intracranial hemorrhage and stroke/systemic embolism were low and similar among those with WRF and without WRF (0.90%/year vs 0.69%/year; $P = 0.3161$). The authors are hailed for their endeavors to present real-world data beyond the constraints of a clinical trial on utilization of DOACs in patients with AF and renal dysfunction. Despite not incorporating a valid predictive model, the finding of comparable proportions of patients with low CrCl at baseline, advanced age, high CHA2DS2-VASc score, frailty, history of heart failure, stroke, and diabetes mellitus in those with WRF and in those with adverse clinical outcomes (stroke and major bleeding) reiterates outcomes from similar studies.[9] Lastly, discontinuation of Edoxaban altogether was more prevalent than dosage adjustment based on renal function. The authors duly recognize the significant limitations of missing data with a substantial number of patients on Edoxaban (~31%) excluded from the analysis. Furthermore, residual confounding, possibility of lower adherence rates, and underreporting of events in registries, as well as the inability to study the temporal relation of WRF and clinical outcomes, impart an exploratory nature to the conclusions. Nevertheless, it would be exciting to see longer follow-up data from the ETNA-AF registry.

The study does not probe anticoagulation for AF in patients on dialysis, and the existing literature is of a conflicting nature. The VALKYRIE trial showed superiority of xarelto vs VKA. The AXADIA-AFNET 8 trial of apixaban 2.5 mg vs VKA found no difference in safety and efficacy outcomes, and despite anticoagulation, end-stage renal disease patients remained at high risk for cardiovascular events, bleeding, and death. Similarly, an observational study reported a significantly higher incidence of fatal or intracranial bleeding events with apixaban vs no anticoagulation.[10]

Thus, despite guidelines recommending dose modification based on CrCl, the hesitation to use DOACs in moderate to severe CKD has led to off-label dosing. This necessitates attention, as there have been concerning reports linking underdosing in CKD to a higher risk of stroke and thromboembolism,[11] including a 5-fold higher risk of stroke with low-dose vs standard-dose apixaban.[12] A United States Renal Data System study found that standard-dose apixaban was better at lowering stroke, systemic embolism, and death compared to low-dose apixaban and VKA.[13]

THE PATH FORWARD

In patients with mild CKD, decisions regarding DOAC dosing are largely based on possible drug interactions that involve the P-glycoprotein pathway. Navigating the risks of stroke and major bleeding in patients with AF and moderate to severe CKD is not straightforward. Predictive tools such as the CHA_2DS_2-VASc score demonstrate poor model performance to quantify the risk of stroke in moderate-to-severe CKD. Likely due to WRF over time, the increased risk of both stroke and bleeding makes a binary variable less interpretable over time. It is essential to create predictive models for different renal function levels, study the ideal frequency of CrCl monitoring, and determine the preferred DOAC in CKD. While we await the results of ongoing SAFE-D (NCT03987711), AVKDIAL (NCT02886962), and DANWARD (NCT03862859) trials for patients with end-stage renal disease, there is an urgent need for an adequately powered head-to-head comparison of DOACs in moderate to severe CKD. The emerging data on nonpharmacological therapies, like left atrial appendage closure, is worth considering in this population. Until we learn more, it is reasonable to follow guidelines where possible and practice shared decision-making with an individualized, patient-centered approach in uncertain clinical situations.

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